WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/00, 38/12, 38/14, C07K 9/00 | A1

(11) International Publication Number: WO 97/38702

(43) International Publication Date: 23 October 1997 (23.10.97)

(21) International Application Number: PCT/US97/05659

(22) International Filing Date: 7 April 1997 (07.04.97)

(30) Priority Data:

60/015,330	12 April 1996 (12.04.96)	US
60/031,736	25 November 1996 (25.11.96)	US

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(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COVALENTLY-LINKED GLYCOPEPTIDE DIMERS

(57) Abstract

The present invention is directed to certain glycopeptide dimers in which two glycopeptide units are covalently linked to one another through a modifiable amine on a saccharide. These dimers are useful as antibacterials, especially for the control of gram positive bacteria; the compounds are particularly useful for the control of resistant bacterial strains, such as vancomycin-resistant-enterococci ("VRE").

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COVALENTLY-LINKED GLYCOPEPTIDE DIMERS

The present invention is directed to glycopeptide dimers covalently linked to one another through an amine function of an amino sugar. The invention is further directed to antibacterial methods employing, and pharmaceutical formulations comprising, such glycopeptide dimers.

Glycopeptides are a class of antibiotics; see, e.g., "Glycopeptide Antibiotics", edited by Nagarajan (Marcel Dekker, Inc., 1994). Two of them, vancomycin and teicoplanin, are sold as antibacterial products for the control of gram positive bacterial infections. Vancomycin, the earlier-discovered of the two, was used for several decades with no bacterial resistance emerging. However, in the late 1980s, resistance was detected (Lancet I, 1988, 57-88). Such resistance has increased in the years since then; see "Nosocomial Enterococci resistant to Vancomycin -- United States, 1989-1993", MMWR Morbid Mortal Wkly. Rep. (Centers for Disease Control and Prevention). Resistance can be to either or both of these antibiotics, and/or also to methicillin. Resistant organisms have become common in nosocomial settings, presenting special risks for immunocompromised persons. Resistant bacteria present a formidable challenge to society.

The present invention provides a new tool in the armamentorium for controlling resistant bacteria.

The present invention is directed to glycopeptide dimers which are covalently linked through an amine function of an

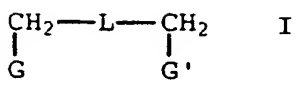
amino sugar. The identity of the glycopeptide is not critical, except that it comprises a modifiable amine on a sugar. Preferred glycopeptides are those of the vancomycin type, also known as dalbaheptides (J. Antibiotics, Dec., 1989, page 1892).

Representative glycopeptides include:

vancomycin,
A82846A,
A82846B,
A82846C,
PA-42867-A,
PA-42867-C,
PA-42867-D,
A83850A,
A83850B,
actinoidin,
avoparcin,
galacardin,
helevecardin, and
M47767.

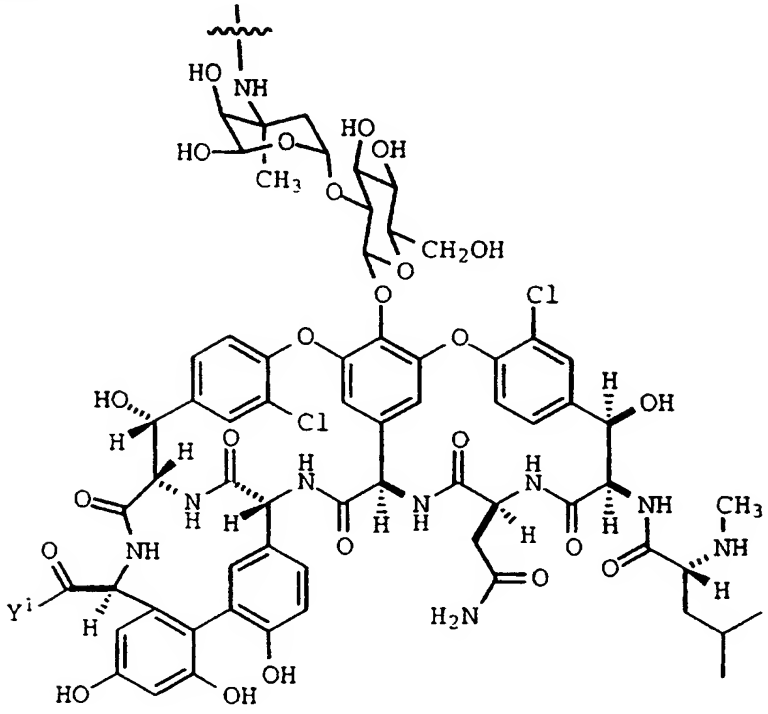
The linking group which functions to covalently link the two glycopeptide units is similarly not critical. The present dimers are most conveniently prepared by the reaction of the glycopeptide and a bisaldehyde, followed by reduction. Therefore, the linking group is the chemical unit internal to the aldehyde groups of any bisaldehyde.

In one embodiment, the present invention is directed to specific dimer compounds defined by Formula I:

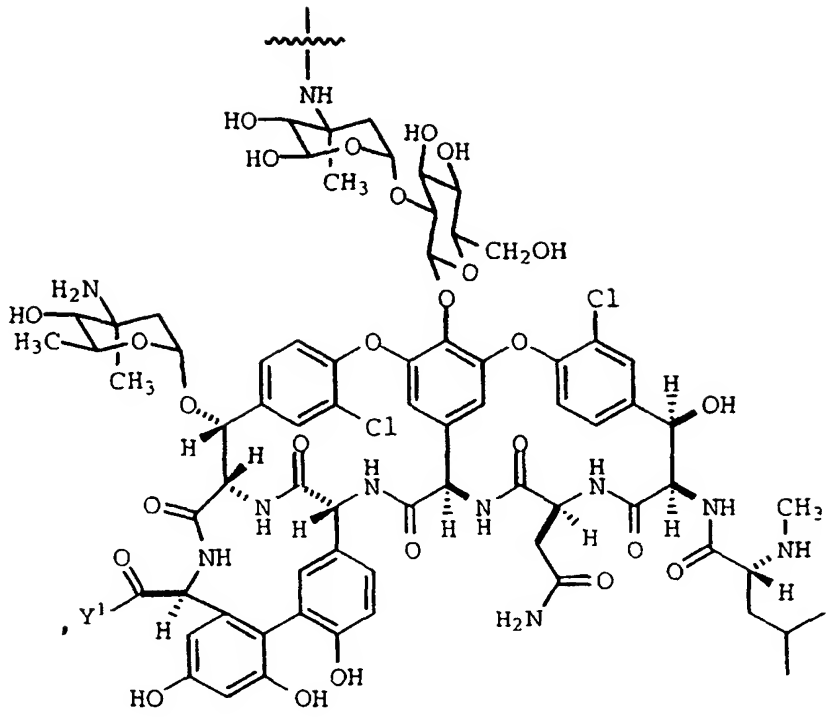


I

In the above formulae, each of G and G' is independently selected from the group consisting of deshydrovancomycin of the formula:



and deshydroA82846B of the formula:



wherein Y^1 is OH or $-N(Y^2)Y^2$ and Y^2 is defined as follows:

(1) each Y^2 independently represents

hydrogen,

alkyl of C_1-C_{10},

cycloalkyl of C_5-C_6,

cycloalkenyl of C_5-C_6,

naphthyl,

biphenylyl,

radical of the formula $-Y^3-(Y^4)_{0,\ 1,\ or\ 2}$, wherein Y^3 is loweralkyl of C_1-C_6 optionally substituted by from one to three substituents, each of which is independently selected from the group consisting of halo, nitro, cyano, alkoxy, haloalkyl, and haloalkoxy; and Y^4 is $-N(Y^5)Y^5$ wherein Y^5 is

independently hydrogen or loweralkyl of C_1-C_4, or Y^4 is phenyl or phenyl substituted with from one to three substituents, each of which is independently

halo,

nitro,

loweralkyl of C_1-C_4,

cycloalkyl of C_5-C_6,

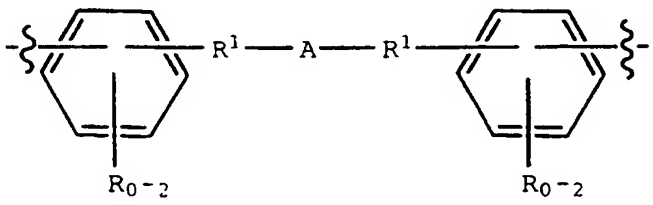
loweralkoxy of C_1-C_4,

haloloweralkyl of C_1-C_4, or

haloloweralkoxy of C_1-C_4; or

(2) one Y^2 is hydrogen and the other Y^2 is (2-furanon-3-yl); or

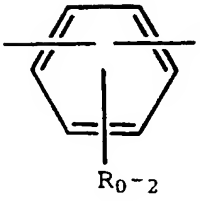
(3) both Y^2s are taken together with the nitrogen and constitute a five- to seven-membered heterocyclic ring optionally containing in addition to the indicated nitrogen atom one additional hetero ring atom which is nitrogen, oxygen, or sulfur, and which heterocyclic radical can be unsubstituted or substituted with from one or two substituents, each of which is loweralkyl of C_1-C_2, loweralkoxy of C_1-C_2, phenyl, benzyl, or C_1-C_6-alkanoyl; and L is a divalent linking radical of the formula A:

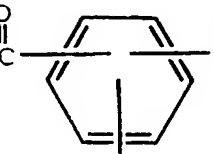
A. 

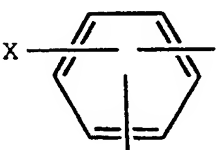
wherein A is:

alkylene of C_1-C_{16},

(alkylene of C_1-C_4-X')$_q$-alkylene of C_1-C_4, wherein q is 1-3,

alkylene of C_1-C_8-X'  X'-alkylene of C_1-C_8;

alkylene of C_1-C_2-X-C  C-X-alkylene of C_1-C_2, or

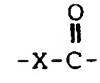
alkylene of C_1-C_2-C-X  X-C-alkylene of C_1-C_2;

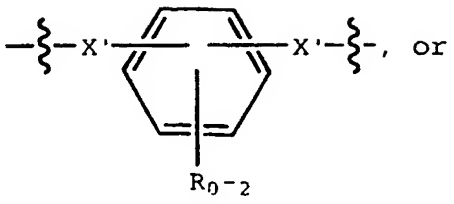
each R^1 is independently

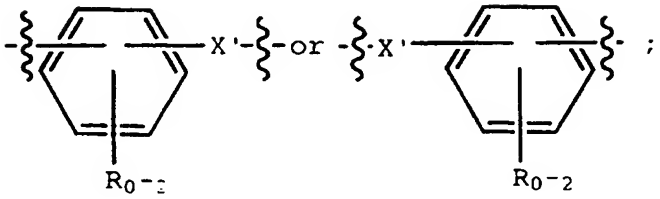
CH_2,

O,

S,





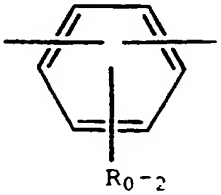


wherein each R independently represents halo, loweralkyl of C_1-C_6, loweralkoxy of C_1-C_6, phenyl, or phenyl substituted by from 1 to 2 substituents, each of which is independently halo, loweralkyl of C_1-C_6, or loweralkoxy of C_1-C_6; each X is independently -O- or -N- wherein R^2 is H or loweralkyl of

C_1-C_4; and each X' is independently -O-, -S-, or -N- wherein R^2 is as defined above; or L is a divalent linking radical of the formula B:

B. -alkylene of C_1-C_8-R^3-X"-R^3-alkylene of C_1-C_8-

wherein X" represents alkylene of C_1-C_4 or a phenylene of the formula



wherein R is as defined above; and each R^3 is independently CH_2 or O. Salts of the foregoing dimers can be used.

In compounds of Formula I, the glycopeptide units, G and G', may be identical or different. Any "alkylene" of C_2 or higher can be straight chain or branched.

Certain compounds are preferred. Symmetrical compounds (G=G' and/or both R^1 are identical), are preferred for their more efficient synthesis.

Antibacterial activity is enhanced by employing preferred "L" groups. Preferences include the following, individually and in any combination:

L = a linking radical of formula A

L = a linking radical of formula B wherein the carbon attached to $-CH_2-G$ or to $-CH_2-G'$ is branched

R^1 = O

A = alkylene of C_1-C_{16}, especially straight-chain and especially C_6-C_{12};

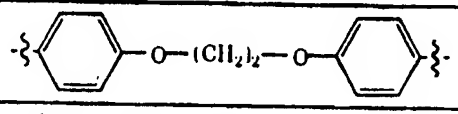
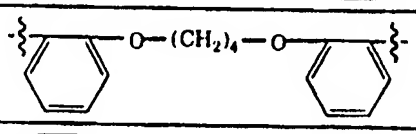
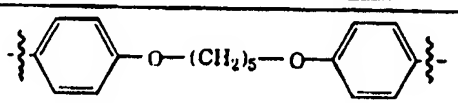
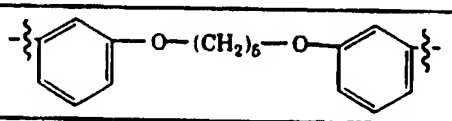
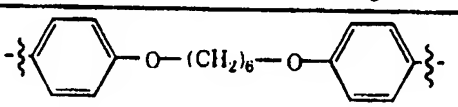
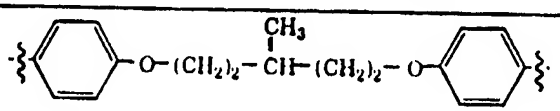
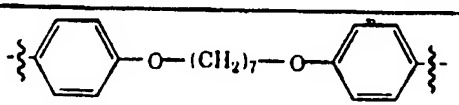
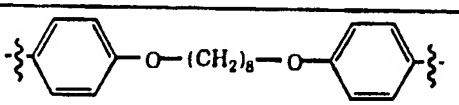
A = (alkylene of $C_1-C_4-X')_q$-alkylene of C_1-C_4, especially wherein X'=O; the alkylene is $-(CH_2)_2-$; and q=2;

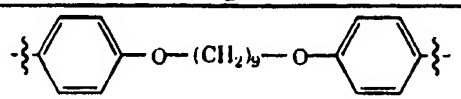
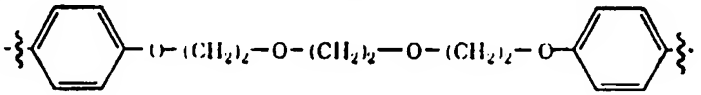
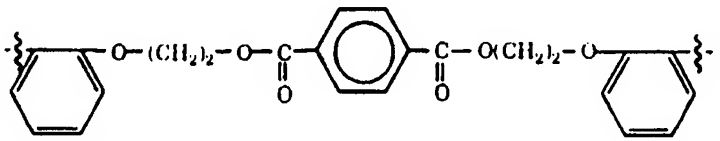
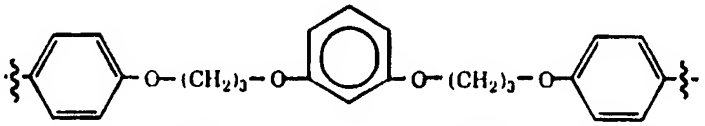
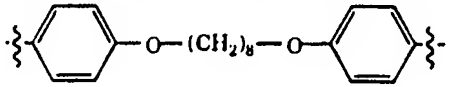
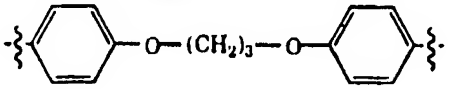
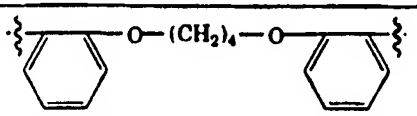
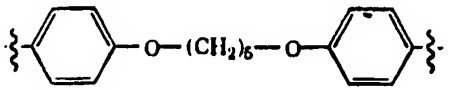
R = phenyl and substituted phenyl, especially chlorophenyl; and especially when R has this value on a phenyl ring within "A".

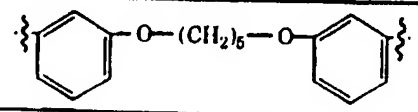
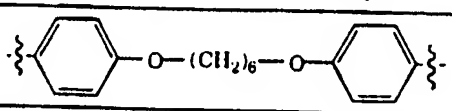
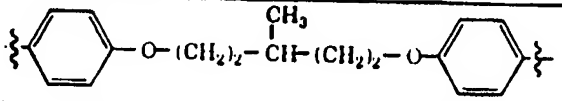
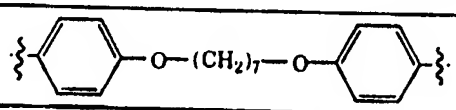
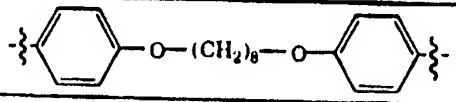
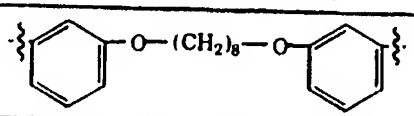
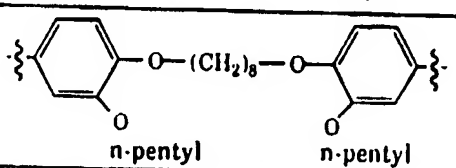
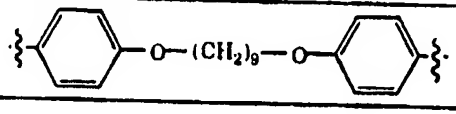
Other preferences will be apparent from the further teachings herein.

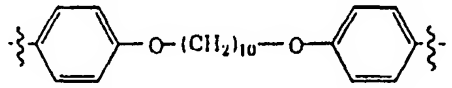
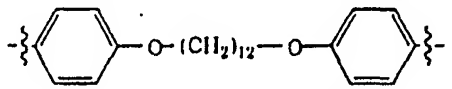
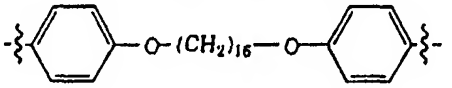
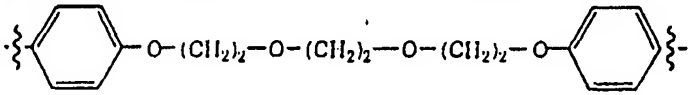
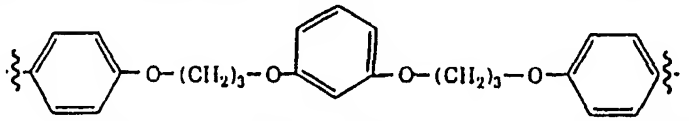
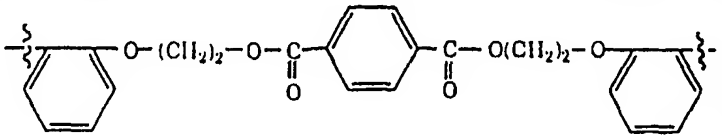
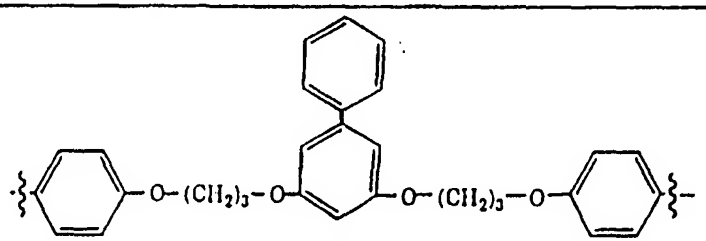
Representative dimers of Formula I are set forth in following TABLE 1.

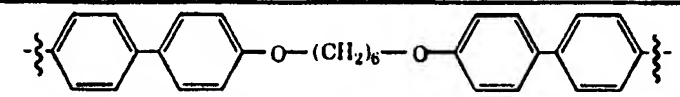
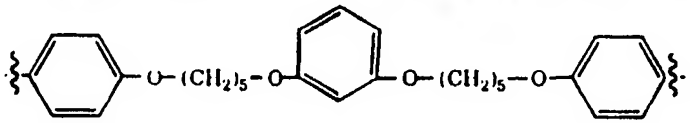
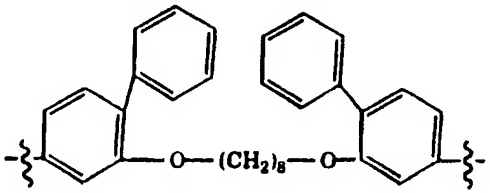
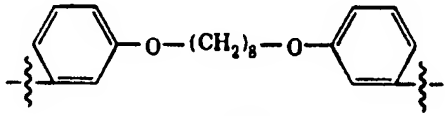
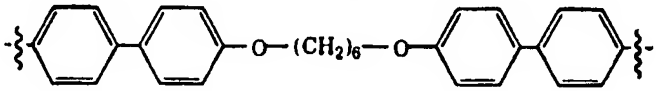
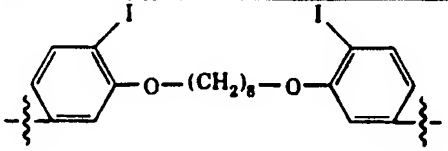
TABLE 1

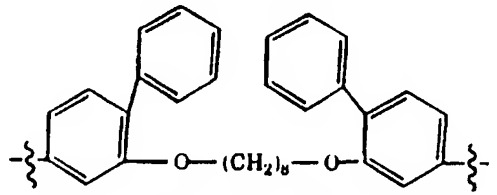
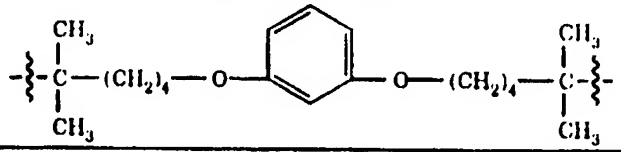
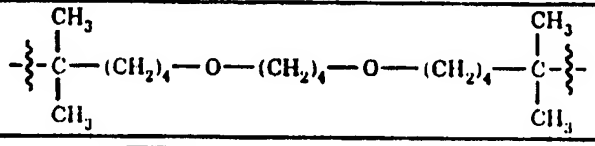
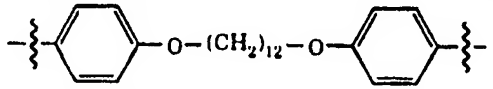
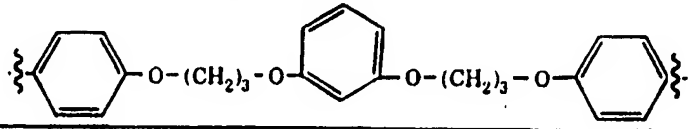
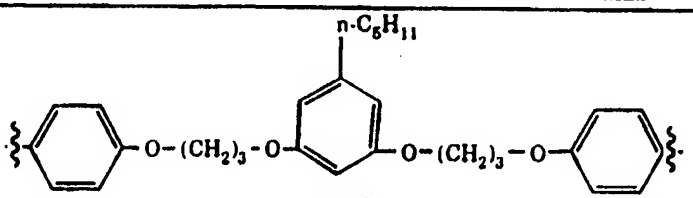
Ex. #	G	G'	L	Name
1	Vanco	Vanco		1,2-ethanediyl-bis-[(oxy-4,1-phenylene)methylene]-bis-[vancomycin]
2	Vanco	Vanco		1,4-butanediyl-bis-[(oxy-2,1-phenylene)-methylene]-bis [vancomycin]
3	Vanco	Vanco		1,5-pentanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
4	Vanco	Vanco		1,5-pentanediyl-bis-[(oxy-3,1-phenylene)-methylene]-bis-[vancomycin]
5	Vanco	Vanco		1,6-hexanediyl-bis-[oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
6	Vanco	Vanco		[3-methyl-1,5-pentanediyl-bis[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
7	Vanco	Vanco		1,7-heptanediyl-bis-[oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
8	Vanco	Vanco		1,8-octanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]

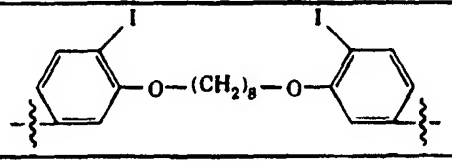
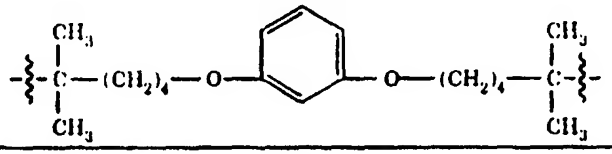
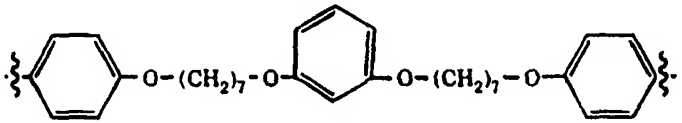
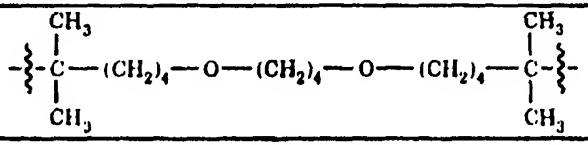
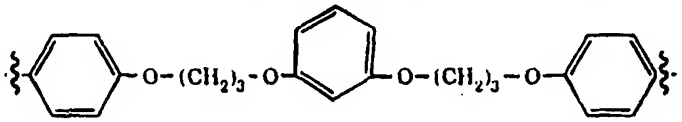
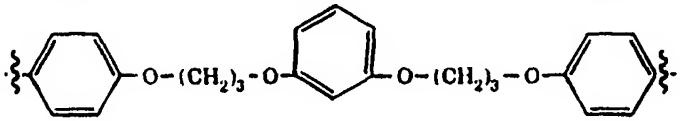
Ex. #	G	G'	L	Name
9	Vanco	Vanco		1,9-nonanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
10	Vanco	Vanco		1,2-ethanediyl-bis-[oxy-1,2 ethyleneoxy-4,1-phenylene]-methylene]bis-[vancomycin]
11	Vanco	Vanco		1,4-phenylene-bis-[(carbonyloxy-1,2-ethylene-oxy-2,1-phenylene)]-methylene]-bis-[vancomycin]
12	Vanco	Vanco		1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)]-methylene]-bis-[vancomycin]
13	A82846B	Vanco		1,8-octanediyl-bis-[(oxy-4,1-phenylene)-methylene]-[vancomycin][A82846B]
14	A82846B	A82846B		1,3-propanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
15	A82846B	A82846B		1,4-butanediyl-bis-[(oxy-2,1-phenylene)-methylene]-bis-[A82846B]
16	A82846B	A82846B		1,5-pentanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]

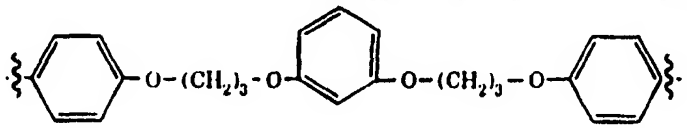
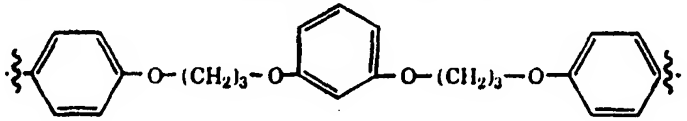
Ex. #	G	G'	L	Name
17	A82846B	A82846B		1,5-pentanediyl-bis-[(oxy-3,1-phenylene]-methylene]-bis-[A82846B]
18	A82846B	A82846B		1,6-hexanediyl-bis-[(oxy-4,1-phenylene) methylene]-bis-[A82846B]
19	A82846B	A82846B		[3-methyl-1,5-pentanediyl]-bis[(oxy 4,1-phenylene)-methylene]-bis-[A82846B]
20	A82846B	A82846B		1,7-heptanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
21	A82846B	A82846B		1,8-octanediyl-bis-[(oxy-4,1-phenylene)-methylene-bis[A82846B]
22	A82846B	A82846B	* HCl salt	* HCl salt
23	A82846B	A82846B		1,8-octanediyl-bis-[(oxy-3,1-phenylene)-methylene]-bis-[A82846B]
24	A82846B	A82846B		1,8-octanediyl-bis-[(oxy-3-n-pentyloxy-4,1-phenylene)methylene]-bis[A82846B]
25	A82846B	A82846B		1,9-nonanediyl-bis-[(oxy-4,1-phenylene]-methylene)-bis-[A82846B]

Ex. #	G	G'	L	Name
26	A82846B	A82846B		1,10-decanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
27	A82846B	A82846B		1,12-dodecanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
28	A82846B	A82846B		1,16-hexadecanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[A82846B]
29	A82846B	A82846B		1,2-ethanediyl-bis-[(oxy-1,2-ethyleneoxy-4,1-phenylene)methylene]--bis[A82846B]]
30	A82846B	A82846B		1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]--bis[A82846B]
31	A82846B	A82846B		1,4-phenylene-bis-[(carbonyloxy-1,2-ethyleneoxy-2,1-phenylene)methylene]-bis[A82846B]
32	A82846B	A82846B		1,3-[5-biphenylyl-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[A82846B]

Ex. #	G	G'	L	Name
33	A82846B	A82846B		1,6-hexanediylbis[oxy-[4,4'-biphenylene]-methylene]bis (A82846B)
34	A82846B	A82846B		1,3-phenylenebis[oxy-1,5-n-pentyleneoxy [4,1-phenylene]methylene] bis (A82846B)
35	A82846B	A82846B		1,8-octanediylbis[oxy-4-phenyl-[3,1-biphenylene]-methylene]bis (A82846B)
36	Vanco	Vanco		1,8-octanediylbis-[(oxy-[3,1-phenylene)-methylene]-bis[vancomycin]
37	Vanco	Vanco		1,6-hexanediylbis[oxy-[4,4'-biphenylene]-methylene]-bis-[vancomycin]
38	Vanco	Vanco		1,8-octanediylbis-[(oxy-4-iodo-3,1-phenylene)methylene]bis-[vancomycin]

Ex. #	G	G'	L	Name
39	Vanco	Vanco		1,8-octanediylbis-[(oxy-4-phenyl-[3,1-phenylene]-methylene]bis-[vancomycin]
40	Vanco	Vanco		1,3-phenylene-bis-[oxy-5-methyl-5,1-hexylene]-bis-[vancomycin]
41	Vanco	Vanco		1,4-butanediylbis-[oxy-5-methyl-5,1-hexylene]-bis-[vancomycin]
42	Vanco	Vanco		1,12-dodecanediyl-bis-[(oxy-4,1-phenylene)-methylene]-bis-[vancomycin]
43	Vanco	Vanco		1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis-[vancomycin].3HCl salt
44	Vanco	Vanco		5-n-pentyl-1,3-phenylene-bis[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis-[vancomycin]

Ex. #	G	G'	L	Name
45	A82846B	A82846B		1,8-octanediylbis-[(oxy-4-iodo-3,1-phenylene)methylene] bis-[A82846B]
46	A82846B	A82846B		1,3-phenylene-bis-[-oxy-[5-methyl-5,1-hexylene]-bis[A82846B]
47	A82846B	A82846B		1,3-phenylene-bis-[(oxy-1,7-n-heptyleneoxy-4,1-phenylene)methylene]-bis-[A82846B]
48	A82846B	A82846B		1,4-butanediylbis-[oxy-5-methyl-5,1-hexylene]-bis-[A82846B]
49	A82846B	A82846B		1,3-phenylene-bis[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[A82846B]
50	A82846B, (3-dimethylamino propyl)-amide	A82846B		1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene] A82846B/A82846B, (3-dimethylaminopropyl)amide

Ex. #	G	G'	L	Name
51	A82846B, (3-dimethylamino propyl)-amide	A82846B, (3-dimethyl amino propyl)-amide		1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis-[A82846B,(3-dimethylaminopropyl)-amide]
52	A82846B, desleucyl	A82846B, desleucyl		1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene]methylene]--bis[desleucylA82846B]

The dimers of the present invention are prepared by reacting a glycopeptide with a bisaldehyde to form an intermediate Schiff base, which is subsequently reduced to obtain the dimers.

Many bisaldehydes are known compounds. They can be prepared by techniques known to those skilled in the art, per various references;

J. Org. Chem., **26**, 474, (1961)

J. Het. Chem., **27**, 1007 (1990)

J.A.C.S., **73**, 1872 (1951)

J.A.C.S., **109**, 2260 (1987)

J. Chem. Soc. Perkin I, 189 (1983)

Syn. Comm., **18(12)**, 1379 (1988)

Chem. Letters, 587 (1995)

Macromolecules, 6045 (1992);

J. Chem. Soc. Chem. Comm. 1463 (1991)

J. Polym. Sci. Part A. Polymer Chem. 31(12) 2899 (1993)

J. Chem. Res. Synop. (8), 296 (1994)

Farmco Ed. Sci. 15, 468 (1960)

Makromol. Chem. 191 (4) 815 (1990)

J. Polym. Sci. Part A. Polymer Chem. 29(3) 361 (1991)

Makromol. Chem. 65, 54 (1963)

The reaction of bisaldehyde with glycopeptide is carried out in accordance with prior art condensations of amine and aldehyde to form Schiff bases, and their subsequent reduction.

Thus, the present condensation is typically conducted in a polar solvent, such as dimethylformamide or methanol, or a mixture of polar solvents. The reaction goes forward over a range of temperatures, such as from 25°C to 100°C, but is preferably conducted at temperatures of about 60°C to 70°C. The reaction is preferably conducted under an inert atmosphere, such as nitrogen or argon. The reaction requires two molecular proportions of glycopeptide and one molecular proportion of bisaldehyde.

The reaction yields a Schiff base of the formula

G=CH-L-CH=G'.

The Schiff base is subsequently reduced. Preferably, the reduction is conducted in the same reaction mixture in a polar solvent, and employing a chemical reducing agent. Metal borohydrides, such as sodium borohydride and sodium cyanoborohydride are preferred. The reaction goes forward over a range of temperatures, such as from about 25°C to about 100°C; preferably, the reaction is conducted at about 60°C to 70°C.

The product, or mixture of products, can be isolated and purified if desired in a conventional manner, such as by HPLC. Characterization of products is best accomplished by Fast Atom Bombardment Mass Spectroscopy (FAB•MS).

In addition to the foregoing synthetic route, compounds of the present invention can be prepared in an alternate route. In this alternate route, a dimer is prepared by the foregoing synthetic route, and further changes to the structure of the glycopeptide are made subsequently. This

approach to synthesizing the present dimers is illustrated by Preparations 6-8 below. In Preparations 6-7, a dimer of the present invention is reacted with an amine to convert the acid of the glycopeptide to an amide ($Y^1 = -N^{Y^2}_{Y^2}$). In Preparation 8, a dimer of the present invention is subjected to Edman degradation to obtain the corresponding desleucyl dimer. Other modifications of the glycopeptide portion of a dimer can likewise be made. Techniques for such modifications are known to those skilled in the art; see Glycopeptide Antibiotics, supra, and references cited therein. This volume is incorporated herein by reference.

When it is desired to employ a salt, a compound of Formula I can be reacted with a mineral or organic acid or an inorganic base, in techniques well known to those skilled in the art. Pharmaceutically-acceptable salts are preferred.

The following examples report preparations of illustrative dimers.

The HPLC procedures reported in these examples were as follows:

Analytical ("Conditions A"): Reactions were monitored by analytical HPLC using a Waters μBondapak C_{18} column (3.9x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH_3CN - 95% buffer to 80% CH_3CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H_3PO_4.

Preparative ("Conditions B"): Crude reaction mixtures were purified by preparative HPLC using a Waters C_{18} Nova-Pak

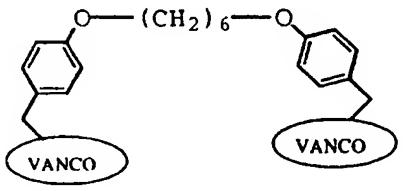
column (40x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH_3CN - 95% buffer to 80% CH_3CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H_3PO_4. The desired fractions were subsequently desalted with a Waters C_{18} Sep-Pak (35 cc) followed by lyophilization. Alternatively, a buffer containing 0.1% TFA in H_2O can be used, in which case the TFA salt is obtained directly after lyophilization.

Compounds were desalted as follows. A Waters Sep-Pak cartridge was pre-wet with methanol (2-3 column volumes) then conditioned with water (2-3 column volumes). The sample, dissolved in a minimum volume of water, was loaded onto the Sep-Pak column which was then washed with water (2-3 column volumes) to remove the unwanted salts. The product was then eluted with an appropriate solvent system, typically 1:1 CH_3CN/H_2O, CH_3CN, and/or methanol. The organic solvent component was removed *in vacuo* and the resulting aqueous solution lyophilized to give the final product.

Preparation 1:

Synthesis of Example 5, 1,6-hexanediylbis[(oxy-4,1-phenylene)methylene]bis[vancomycin]

(one-pot synthesis of vancomycin dimer)



A dry 100 mL round bottom flask was charged with vancomycin•HCl (250 mg, 0.168 mmol.), and 1,6-bis(4'-formylphenoxy)-n-hexane (101 mg, 0.310 mmol.). Anhydrous DMF (6 mL) was added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 3.5 hours, sodium cyanoborohydride (80 mg, 1.3 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour. The reaction mixture was cooled, and stored at 0°C overnight.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, 1,6-hexanediylbis[(oxy-4,1-phenylene)methylene]bis[vancomycin] was obtained (24.3 mg, 0.008 mmol., 10.0 % yield) as a white powder.

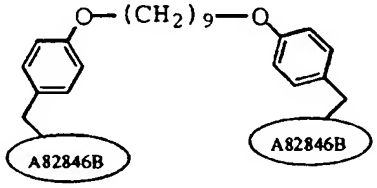
HPLC (conditions A) retention time: 13.6 min.

FABMS shows peak of (M+6H) at 3195.

Preparation 2:

Synthesis of Example 25, 1,9-nonanediylbis[(oxy-4,1-phenylene)methylene]bis[A82846B]

(one-pot synthesis of A82846 dimer)



A dry 100 mL round bottom flask was charged with A82846B·tri-acetate salt (278 mg, 0.157 mmol.), and 1,9-bis-(4'-formylphenoxy)-n-nonane (103.7 mg, 0.282 mmol.). Anhydrous DMF (15 mL) and anhydrous MeOH (15 mL) were added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 3.5 hours, sodium cyanoborohydride (68 mg, 1.08 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (5 mL) and HOAc (0.5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After

lyophilization, 1,9-nonanediylbis[(oxy-4,1-phenylene)methylene]bis[epivancomycin] was obtained (25.7 mg, 0.007 mmol., 9.3 % yield) as a white powder.

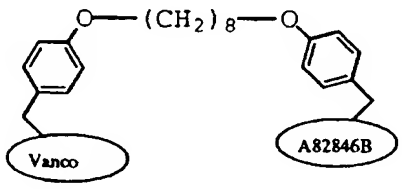
HPLC (conditions A) retention time: 14.9 min.

FABMS shows peak of (M+5H)at 3522.

Preparation 3:

Synthesis of Example 13, 1,8-octanediylbis[(oxy-4,1-phenylene)methylene][vancomycin][A82846B]

(synthesis of hybrid dimer)



A dry round bottom flask was charged with vancomycin•HCl (75 mg, 0.052 mmol.), and N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B (50 mg, 0.026 mmol.) (see Preparation 4). Anhydrous DMF (6 mL) was added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 5 hours, sodium cyanoborohydride (59 mg, 0.93 mmol.) was added in one portion, and the reaction mixture was maintained at 70°C for one additional hour. The reaction mixture was cooled, and stored at 0°C overnight.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (5 mL) and HOAc (0.5 mL). The resulting solution was purified by

preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, 1,8-octanediylbis[(oxy-4,1-phenylene)methylene][vancomycin][A82846B] was obtained (5.2 mg, 0.002 mmol., 7.6 % yield) as a white powder.

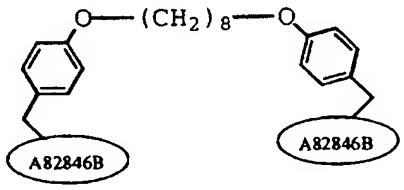
HPLC (conditions A) retention time: 14.5 min.

FABMS shows peak of (M+6H) at 3364.

Preparations 4 & 5:

Synthesis of Example 47, N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B, and Example 21, 1,8-octanediylbis[(oxy-4,1-phenylene)methylene]bis[A82846B]

(two-step synthesis of A82846 dimer)



A dry flask was charged with A82846B·tri-acetate salt (5.0 g, 0.003 mol.), and 1,8-bis(4'-formylphenoxy)-n-octane (1.93 g, 0.006 mol.). Anhydrous DMF (300 mL) and anhydrous MeOH (300 mL) were added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 3.75 hours, sodium cyanoborohydride (0.76 g, 0.012 mol.) was added in one portion, and the reaction mixture was maintained at

70°C for one additional hour. The reaction was cooled and stored at 0°C overnight.

The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (200 mL) and HOAc (5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~ 1.5 mL, and desalted. After lyophilization, N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B was obtained (387.4 mg, 0.2 mmol., 6.6 % yield) as a white powder.

HPLC (conditions A) retention time: 19.9 min.

FABMS shows peak of (M+3H)at 1932.

A dry flask was charged with N^4-(4-(8-(p-formylphenoxy)-n-octyloxy)benzyl)A82846B (20.0 mg, 0.01 mmol), and A82846B (32.9 mg, 0.021 mmol). Anhydrous DMF (3 mL) and anhydrous MeOH (3 mL) were added to the flask and the resulting mixture was stirred under N_2 and heated to 70°C. After 2 hours, sodium cyanoborohydride (5.0 mg, 0.079 mmol) was added in one portion, and the reaction mixture stirred an additional 0.25 hours.

The reaction mixture was then concentrated in vacuo to give a residue which was redissolved in 1:1 H_2O:CH_3CN (5 mL). The resulting solution was purified by preparatory HPLC (conditions D). The desired fraction, as determined by analytical HPLC (conditions A), were concentrated in vacuo to ~1.5 mL, and desalted. After lyophilization, 1,8-

octanediylbis[(oxy-4,1-phenylene)methylene]bis[A82846B] was obtained (3.0 mg, 0.001 mmol, 8.6 % yield) as a white powder.

HPLC (conditions A) retention time: 13.6 min.

FABMS shows peak of (M+5H) at 3508.

Preparations 6 & 7:

Synthesis of Example 50, 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]A82846B/A82846B, (3-dimethylaminopropyl)amide,

and Example 51, 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis[A82846B, (3-dimethylaminopropyl)amide]

A dry round bottom flask was charged with 1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]--bis[A82846B] (50.0 mg, 0.014 mmol) and 1 mL DMSO. PyBOP (14.5 mg, 0.028 mmol) and 3-dimethylaminopropylamine (2.8 mg, 0.028 mmol) were added and the reaction was stirred at room temperature under nitrogen for one hour. The reaction mixture was then concentrated in vacuo to give a residue which was re-dissolved in 1:1 H_2O:CH_3CN (5 mL). The resulting solution was purified by preparatory HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A) were concentrated in vacuo to ~ 1.5 mL, and desalted as in previous examples. After lyopholization 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis[A82846B,(3-dimethyl-aminopropyl)amide] (6.9 mg, 13.1% yield) and 1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)-

methylene]A82846B/A82846B,(3-dimethylaminopropyl)amide (6.6 mg, 12.8% yield) were obtained as white powders.

1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)methylene]bis[A82846B,(3-dimethylaminopropyl)-amide]

HPLC (conditions A) retention time: 13.2 min.

FABMS shows peak of (M+9H) at 3761.

1,3-phenylenebis[oxy-1,3-n-propylene-oxy-4,1-phenylene)-methylene]A82846B/A82846B,(3-dimethylaminopropyl)amide

HPLC (conditions A) retention time: 13.7 min.

FABMS shows peak of (M+6H) at 3674.

Preparation 8:

Synthesis of Example 52, 1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[desleucylA82846B]

1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[A82846B] (165.8 mg, 0.0462 mmol) was dissolved in 15 mL H_2O - pyridine (1:1 v/v) and treated with phenyl isothiocyanate (30 µl, 0.25 mmol). The resulting mixture was stirred at room temperature for 1.5 hours at which time HPLC analysis (conditions A) indicated complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* to give the crude bisthiourea derivative as a white powder.

The crude thiourea intermediate was suspended in 15 mL CH_2Cl_2, cooled to 0°C, then treated with trifluoroacetic acid (0.20 mL). After 1 hour the reaction mixture was warmed to room temperature and stirred an additional 1 hour. An additional 0.20 mL trifluoroacetic acid was added and the mixture was stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the crude product was purified by preparative HPLC (conditions B). The desired fractions, as determined by analytical HPLC (conditions A) were concentrated *in vacuo* to ~ 1.5 mL, and desalted as in previous examples to give 10.2 mg (7% yield) of 1,3-phenylene-bis-[(oxy-1,3-n-propyleneoxy-4,1-phenylene)methylene]-bis[desleucylA82846B] as a white powder.

FAB-MS: obtained 3333 (M+4)

HPLC retention time (conditions A): 15.1 min.

Details concerning the synthesis of all of the compounds of TABLE 1, as well as identifying characteristics, are presented in TABLE 2.

TABLE 2

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+x H
1	1,2-bis(4-formylphenoxy)-n-ethane	11.5	1.86	3136	3
2	1,4-bis(2-formylphenoxy)-n-butane	11.8	0.79	3165	4
3	1,5-bis(4-formylphenoxy)-n-pentane	12.9	5.42	3178	4
4	1,5-bis(3-formylphenoxy)-n-pentane	13.0	4.08	3179	4
5	1,6-bis(4-formylphenoxy)-n-hexane	13.6	9.05	3195	6
6	3-methyl-1,5-bis(4-formylphenoxy)-n-pentane	13.5	4.54	3193	4
7	1,7-bis(4-formylphenoxy)-n-heptane	14.7	5.00	3207	5
8	1,8-bis(4-formylphenoxy)-n-octane	15.5	3.91	3219	2
9	1,9-bis(4-formylphenoxy)-n-nonane	16.4	4.41	3235	4
10	1,2-bis(2-(4-formylphenoxy)-ethoxy)ethane	12.3	1.89	3226	4
11	1,4-bis(2-(p-formylphenoxy)-ethoxy)carbonyl-benzene	13.0	10.50	3331	6
12	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	15.5	3.10	3300	4
13	1,8-bis(4-formylphenoxy)-n-octane	14.5	5.95	3364	4
14	1,3-bis(4-formylphenoxy)-propane	9.4	14.29	3436	4
15	1,4-bis(2-formylphenoxy)-n-butane	10.2	5.91	3452	5

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+x H
16	1,5-bis(4-formylphenoxy)-n-pentane	10.4	3.86	3466	5
17	1,5-bis(3-formylphenoxy)-n-pentane	11.3	22.41	3465	4
18	1,6-bis(4-formylphenoxy)-n-hexane	11.3	5.46	3478	4
19	3-methyl-1,5-bis(4-formylphenoxy)-n-pentane	11.3	8.14	3479	4
20	1,7-bis(4-formylphenoxy)-n-heptane	12.5	5.73	3494	5
21	1,8-bis(4-formylphenoxy)-n-octane	14.0	13.31	3508	5
23	1,8-bis(3-formylphenoxy)-n-octane	14.4	21.23	3508	5
24	1,8-bis(4-formyl-2-n-pentyloxy-phenoxy)-n-octane	20.8	16.91	3680	5
25	1,9-bis(4-formylphenoxy)-n-nonane	14.9	9.31	3522	5
26	1,10-bis(4-formylphenoxy)-n-decane	15.9	8.87	3535	5
27	1,12-bis(4-formylphenoxy)-n-dodecane	17.7	1.32	3565	6
28	1,16-bis(4-formylphenoxy)-n-hexadecane	20.4	4.05	3625	9
29	1,2-bis(2-(4-formylphenoxy)-ethoxy)ethane	10.2	6.28	3511	4
30	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	15.2	22.96	3589	5
31	1,4-bis(2-(p-formylphenoxy)-ethoxy)carbonyl-benzene	11.7	24.94	3615	5

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+xH
32	5-phenyl-1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	16.8	12.88	3664	5
33	1,6-bis(4-(4-formylphenyl)-phenoxy)hexane	16.2	11.58	3633	5
34	1,3-bis(5-(4-formylphenoxy)-n-pentyloxy)-benzene	17.04	9.31	3645	6
35	1,8-bis(2-phenyl-5-formylphenoxy)-octane	18.3	10.83	3662	6
36	1,8-bis(3-formylphenoxy)-n-hexane	15.3	2.1	3221	4
37	1,6-bis(4-(4'-formylphenoxy)-phenoxy)-n-hexane	18.2	6.1	3347	6
38	1,8-bis(3-formyl-2-iodophenoxy)-n-hexane	22.9	2.2	3471	3
39	1,8-bis(2-phenyl-5-formylphenoxy)-n-octane	19.3	2.8	3374	4
40	1,3-bis(6-(2-dimethyl)-1-hexanaloxy)-benzene	15.5	8.2	3229	4
41	1,4-bis(6-(2-dimethyl)-1-hexanaloxy)-butane	13.5	6.1	3209	4
42	1,12-bis(4-formylphenoxy)-n-dodecane	21.6	6.8	3278	5
43	1,3-bis(3-(p-formylphenoxy-n-propyloxy)-benzene	HCL SALT			
44	1,3-bis(3-(p-formylphenoxy-n-propyloxy)-5-n-pentylbenzene	36.6	12.7	3660	8
45	1,8-bis(3-formyl-2-iodophenoxy)-n-octane	17.1	5.4	3762	6

Ex. #	Aldehyde	HPLC * Retention Minutes	% yield	FAB•MS M/Z	M+x H
46	1,3-bis(6-(2-dimethyl)-1-hexanaloxy)-benzene	13.3	15.5	3516	5
47	1,3-bis(3-(p-formylphenoxy-n-heptyloxy)-benzene	19.3	1.4	3701	6
48	1,4-bis(6-(2-dimethyl)-1-hexanaloxy)-butane	13.5	24.8	3495	4
49	1,3-bis(3-(p-formylphenoxy-n-propyloxy)-benzene	HCL SALT			
50	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	13.7	12.8	3674	6
51	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	13.2	13.1	3761	9
52	1,3-bis(3-(p-formylphenoxy)-n-propyloxy)-benzene	15.1	7.0	3333	4

* Conditions A

The present glycopeptide dimers are useful for the treatment of bacterial infections. Therefore, in another embodiment, the present invention is directed to a method for controlling a bacterial infection in a host animal, typically a warm-blooded animal, which comprises administering to the host animal an effective, antibacterial amount of a glycopeptide dimer in which two glycopeptide units are covalently linked to one another through an amine function of an amino sugar. In this embodiment, the dimers can be used to control and treat infections due to various bacteria, but especially gram-positive bacteria. In a preferred

embodiment, the dimers are used to control and treat infections due to bacteria resistant to existing antibacterials. For example, certain bacteria are resistant to methicillin, and yet others are resistant to vancomycin and/or teicoplanin. The present dimers provide a technique for controlling and treating infections due to such resistant bacterial species.

In carrying out this embodiment of the invention, the dimers can be administered by any of the conventional techniques, including the oral route and parenteral routes such as intravenous and intramuscular. The amount of compound to be employed is not critical and will vary depending on the particular compound employed, the route of administration, the severity of the infection, the interval between dosings, and other factors known to those skilled in the art. In general, a dose of from about 0.5 to about 100 mg/kg will be effective; and in many situations, lesser doses of from about 0.5 to about 50 mg/kg will be effective. A compound of the present invention can be administered in a single dose, but in the known manner of antibacterial therapy, a compound of the present invention is typically administered repeatedly over a period of time, such as a matter of days or weeks, to ensure control of the bacterial infection.

Also in accordance with known antibacterial therapy, a dimer of the present invention is typically formulated for convenient delivery of the requisite dose. Therefore, in another embodiment, the present invention is directed to a

pharmaceutical formulation comprising a dimer of Formula I, in combination with a pharmaceutically-acceptable carrier. Such carriers are well known for both oral and parenteral routes of delivery. In general, a formulation will comprise a dimer in a concentration of from about 0.1 to about 90% by weight, and often from about 1.0 to about 3%.

The antibacterial efficacy of the present dimers is illustrated by following TABLES 3 and 4. The minimal inhibitory concentrations (MICs) were determined using a standard broth micro-dilution assay. TABLE 4 presents a comparison of the activity of illustrative compounds against representative vancomycin-resistant and vancomycin-sensitive enterococci (Enterococcus faecium and Enterococcus faecalis, mean geometric MIC (mcg/mL), as determined by the standard broth micro-dilution assay.

TABLE 3
In Vitro Antimicrobial Activity
MIC (mcg/ml)/Compound

Organism	Vancomycin	A82846B	1	2	3	4	5	6	7
Staphylococcus aureus 446	0.5	0.25	4	16	8	8	4	4	2
Staphylococcus aureus 489	0.125	≤0.06	0.5	0.5	0.5	2	0.5	0.25	0.5
Staphylococcus aureus 447	0.5	0.25	16	>64	32	32	16	8	8
Staphylococcus aureus X400	0.5	0.125	1	1	2	2	1	1	1
Staphylococcus aureus X778	0.5	0.125	1	4	2	4	1	1	1
Staphylococcus aureus 491	1	0.25	0.5	0.5	0.25	2	0.25	0.5	0.5
Staphylococcus aureus S13E	0.5	0.125	2	2	2	4	1	2	0.5
Staphylococcus aureus SA1199	0.5	0.125	4	4	32	4	2	4	1
Staphylococcus aureus SA1199A	0.125	≤0.06	0.5	0.125	0.5	1	0.25	0.5	0.25
Staphylococcus aureus SA1199B	0.5	0.125	4	4	16	4	2	4	1
Staphylococcus haemolyticus 109	16	1	8	4	8	8	4	8	2
Staphylococcus haemolyticus 419	8	4	16	>64	16	16	8	8	8
Staphylococcus epidermidis 270	16	0.25	8	>64	16	16	4	4	4
Enterococcus faecium 180	>64	8	0.25	1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecium 180-1	0.5	0.125	0.5	1	0.5	1	0.25	≤0.06	≤0.06
Enterococcus faecalis 2041	2	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5
Enterococcus faecalis 276	1	0.125	0.25	0.25	0.5	0.25	0.5	0.5	1
Enterococcus gallinarum 245	4	0.25	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Haemophilus influenzae RD	>64	>64		>64		>64			
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.5		0.06	0.06	0.06	0.06	0.06	0.06	0.06
Streptococcus pneumoniae P1	0.25		0.06	0.06	0.06	0.06	0.06	0.06	0.06

TABLE 3
In Vitro Antimicrobial Activity
MIC (mcg/ml)/Compound

Organism	8	9	10	11	12	13	14	15	16
Staphylococcus aureus 446	8	1	8	16	8	8	4	4	8
Staphylococcus aureus 489	4	1	4	4	2	2	1	0.25	2
Staphylococcus aureus 447	32	4	16	64	8	16	16	64	>64
Staphylococcus aureus X400	4	1	4	8	2	4	2	0.5	2
Staphylococcus aureus X778	4	1	4	16	2	2	1	0.5	2
Staphylococcus aureus 491	2	0.5	1	0.25	2	1	0.25	0.125	0.5
Staphylococcus aureus S13E	8	2	4	8	4	4	2	1	1
Staphylococcus aureus SA1199	16	1	4	16	4	4	4	1	4
Staphylococcus aureus SA1199A	2	0.25	1	1	1	0.5	0.125	≤0.06	0.5
Staphylococcus aureus SA1199B	8	0.5	4	32	4	4	2	4	2
Staphylococcus haemolyticus 109	8	0.5	4	64	4	1	4	8	1
Staphylococcus haemolyticus 415	8	4	16	64	4	8	16	>64	32
Staphylococcus epidermidis 270	8	2	16	32	4	8	8	64	32
Enterococcus faecium 180	0.125	≤0.06	4	2	≤0.06	0.125	0.25	0.25	0.125
Enterococcus faecium 180-1	0.5	0.25	1	0.25		0.5	≤0.06	0.25	0.5
Enterococcus faecalis 2041	0.25	0.5	0.25	≤0.06	0.25	0.25	0.25	0.125	0.25
Enterococcus faecalis 276	2	1	1	0.5	1	1	0.5	0.5	1
Enterococcus gallinarum 245	0.25	0.06	0.125	0.06	0.06	0.06	0.06	0.06	0.25
Haemophilus influenzae RD	>64	>64	64			>64	>64		>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	8	0.06	0.06	0.06	0.06	0.06	0.06	0.06	1
Streptococcus pneumoniae P1	4	0.06	0.06	0.06	0.06	0.06	0.06	0.125	1

TABLE 3
In Vitro Antimicrobial Activity
MIC (mcg/ml)/Compound

Organism	17	18	19	20	21	22	23	24	25
Staphylococcus aureus 446	4	8	4	4	8	4	2	2	4
Staphylococcus aureus 489	1	4	0.25	2	2	4	1	2	4
Staphylococcus aureus 447	>64	64	32	64	64	32	8	16	64
Staphylococcus aureus X400	1	2	0.5	2	2	4	1	2	2
Staphylococcus aureus X778	2	2	0.5	1	1	1	0.25	2	2
Staphylococcus aureus 491	0.5	0.25	0.25	1	2	2	1	1	2
Staphylococcus aureus S13E	1	2	1	2	1	2	4	2	4
Staphylococcus aureus SA1199	1	2	1	4	1	2	2	2	4
Staphylococcus aureus SA1199A	0.125	0.25	0.125	0.25	0.25	0.5	0.5	1	0.5
Staphylococcus aureus SA1199B	1	1	2	2	1	4	1	2	4
Staphylococcus haemolyticus 105	0.5	0.5	8	2	16	4	4	2	2
Staphylococcus haemolyticus 415	8	16	32	32	8	16	4	4	16
Staphylococcus epidermidis 270	64	16	16	16	8	8	4	4	16
Enterococcus faecium 180	0.125	≤0.06	0.125	≤0.06	0.125	0.25	0.125	1	0.25
Enterococcus faecium 180-1	0.125	0.25	1	1	0.5	0.5		0.5	1
Enterococcus faecalis 2041	0.125	0.25	0.25	≤0.06	0.5	0.5	0.5	1	1
Enterococcus faecalis 276	0.125	0.125	1	0.25	1	1	1	2	1
Enterococcus gallinarum 245	0.06	0.06	0.06	0.06	0.06	0.06	0.125	0.5	0.25
Haemophilus influenzae RD	>64	>64		>64	>64	>64		>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.25	0.25
Streptococcus pneumoniae P1	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.125

TABLE 3
In Vitro Antimicrobial Activity
MIC (mcg/ml)/Compound

Organism	26	27	28	29	30	31	32	33	34
Staphylococcus aureus 446	4	16	>64	16	1	1	16	16	2
Staphylococcus aureus 489	2	8	64	1	1	1	4	4	2
Staphylococcus aureus 447	>64	>64	>64	64	4	8	>64	>64	2
Staphylococcus aureus X400	1	16	32	1	1	0.5	4	8	1
Staphylococcus aureus X778	2	8	32	2	0.5	0.25	2	4	1
Staphylococcus aureus 491	2	8	16	≤0.06	0.25	≤0.06	2	4	0.5
Staphylococcus aureus S13E	2	8	64	4	0.5	0.25	8	8	1
Staphylococcus aureus SA1199	2	8	64	2	1	0.5	8	8	2
Staphylococcus aureus SA1199A	1	4	16	0.5	≤0.06	≤0.06	2	4	0.5
Staphylococcus aureus SA1199B	2	8	64	4	1	0.5	8	16	2
Staphylococcus haemolyticus 109	4	32	32	0.25	0.25	0.25	4	2	0.5
Staphylococcus haemolyticus 419	16	64	64	>64	4	16	8	8	2
Staphylococcus epidermidis 270	8	32	64	32	1	2	16	8	1
Enterococcus faecium 180	0.5	1	8	0.25	0.125	1	1	1	0.5
Enterococcus faecium 180-1	1	1	8	0.5	0.125	≤0.06	2	2	0.25
Enterococcus faecalis 2041	1	4	8	0.125	0.25	≤0.06	2	2	0.125
Enterococcus faecalis 276	2	4	8	0.25	0.5	0.125	2	2	0.5
Enterococcus gallinarum 245	1	2	4	0.06	0.125	0.06	1	0.5	0.25
Haemophilus influenzae RD	>64	>64	>64			>64	>64		>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	4	0.5	64	0.06	0.06	0.06	0.5	2	≤0.06
Streptococcus pneumoniae P1	2	1	64	0.06	0.06	0.06	0.125	2	0.125

TABLE 3
In Vitro Antimicrobial Activity
MIC (mcg/ml)/Compound

Organism	35	36	37	38	39	40
Staphylococcus aureus 446	16	8	8	8	>64	8
Staphylococcus aureus 489	8	2	2	2	>64	2
Staphylococcus aureus 447	>64	16	16	32	>64	32
Staphylococcus aureus X400	4	4	2	4	>64	4
Staphylococcus aureus X778	4	4	2	4	>64	4
Staphylococcus aureus 491	2	1	1	2	>64	1
Staphylococcus aureus S13E	8	4	4	4	>64	8
Staphylococcus aureus SA1199	32	8	4	4	>64	4
Staphylococcus aureus SA1199A	8	1	2	2	>64	1
Staphylococcus aureus SA1199B	8	16	2	4	>64	4
Staphylococcus haemolyticus 105	2	2	8	2	>64	2
Staphylococcus haemolyticus 415	16	8	16	16	>64	32
Staphylococcus epidermidis 270	8	4	8	8	>64	8
Enterococcus faecium 180	2	<.06	1	2	8	0.25
Enterococcus faecium 180-1	1	0.25	1	1	8	0.5
Enterococcus faecalis 2041	2	0.5	2	2	16	<.06
Enterococcus faecalis 276	4	0.25	1	4	32	0.5
Enterococcus gallinarum 245	1	0.06	1	4	8	0.06
Haemophilus influenzae RD		>64	>64	4	>64	
Escherichia coli EC14	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	1	0.06	1	16	8	0.06
Streptococcus pneumoniae P1	1	0.06	1	8	16	0.06

TABLE 3
In Vitro Antimicrobial Activity
MIC (mcg/ml)/Compound

Organism	41	42	43	44	45	46
Staphylococcus aureus 446	32	64	8	8	8	4
Staphylococcus aureus 489	1	32	1	4	2	1
Staphylococcus aureus 447	>64	>64	8	16	32	64
Staphylococcus aureus X400	4	32	2	8	2	1
Staphylococcus aureus X778	8	16	2	4	2	1
Staphylococcus aureus 491	1	8	1	2	2	0.5
Staphylococcus aureus S13E	8	>64	2	16	4	1
Staphylococcus aureus SA1199	16	32	2	8	2	1
Staphylococcus aureus SA1199A	8	16	0.5	1	1	0.125
Staphylococcus aureus SA1199B	8	32	2	16	2	1
Staphylococcus haemolyticus 109	2	16	8	1	4	1
Staphylococcus haemolyticus 419	>64	64	8	8	4	32
Staphylococcus epidermidis 270	32	32	4	4	2	1
Enterococcus faecium 180	2	2	0.125	1	1	0.5
Enterococcus faecium 180-1	1	4	1	0.5	1	<.06
Enterococcus faecalis 2041	0.25	4	0.25	2	1	<.06
Enterococcus faecalis 276	0.5	8	0.25	2	1	0.5
Enterococcus gallinarum 245	1	1	0.06	1	1	0.06
Haemophilus influenzae RD	>64		>64		2	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.06	1	0.06	1	8	0.06
Streptococcus pneumoniae P1	0.06	2	0.06	2	4	0.06

TABLE 3
In Vitro Antimicrobial Activity
MIC (mcg/ml)/Compound

Organism	47	48	49	50	51	52
Staphylococcus aureus 446	16	8	0.5	2	4	8
Staphylococcus aureus 489	8	0.5	0.25	0.5	2	4
Staphylococcus aureus 447	>64	32	1	2	4	16
Staphylococcus aureus X400	16	1	0.5	1	4	8
Staphylococcus aureus X778	8	1	0.5	1	2	4
Staphylococcus aureus 491	8	0.5	<.06	0.5	2	2
Staphylococcus aureus S13E	32	4	1	1	2	16
Staphylococcus aureus SA1199	16	4	1	1	4	8
Staphylococcus aureus SA1199A	4	0.5	0.5	0.25	2	1
Staphylococcus aureus SA1199B	16	2	1	1	2	16
Staphylococcus haemolyticus 105	8	4	1	0.5	2	1
Staphylococcus haemolyticus 415	8	32	2	1	2	8
Staphylococcus epidermidis 270	8	4	0.5	1	1	4
Enterococcus faecium 180	2	1	0.25	1	2	1
Enterococcus faecium 180-1	0.5	0.25	<.06	0.25	0.5	0.5
Enterococcus faecalis 2041	2	0.25	<.06	0.5	0.5	2
Enterococcus faecalis 276	2	0.125	0.25	0.5	1	2
Enterococcus gallinarum 245	2	0.06	0.06	0.5	0.5	1
Haemophilus influenzae RD	>64	>64				
Escherichia coli EC14	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	2	0.06	0.06	0.125	0.5	1
Streptococcus pneumoniae P1	1	0.06	0.06	0.06	0.5	2

TABLE 4

In Vitro Activity Against Enterococci		
Cpd. Number	Vancomycin Resistant Strains	Vancomycin Sensitiv Strains
Vancomycin	282	3.9
A82846B	29	0.22
1	42	1.3
2	27	1.0
3	27	1.5
4	19	2.0
5	11	0.87
6	32	1.3
7	8.0	1.3
8	9.5	0.87
9	9.5	1.2
10	>90	3.0
11	38	1.7
12	4.0	0.66
13	9.5	1.2
14	>64	1.0
15	23	0.87
16	38	1.5
17	4.8	0.57
18	19	1.0
19	19	0.76
20	13	1.0
21	2.8	0.87
22	6.7	0.76
23	1.7	0.5
24	4.8	1.2
25	6.7	1.2
26	4.0	1.5
27	3.4	1.7
28	9.5	6.1
29	38	1.3
30	1.7	0.38
31	27	0.66
32	2.8	1.5
33	2.0	1.5
34	1.7	0.44
35	3.4	2.3
36	5.7	0.66
37	4.8	2.3
38	4.8	2.3
39	8	5.3
40	11.3	0.76
41	64	1
42	2.4	1.2
43	2.4	1.3
44	2	1.2
45	3.4	1.5
46	4.8	0.57
47	6.7	4

TABLE 4

In Vitro Activity Against Enterococci		
Cpd. Number	Vancomycin Resistant Strains	Vancomycin Sensitiv Strains
48	22	0.57
49	2	0.38
50	3.4	0.38
51	2.4	0.38
52	128	4.6

WE CLAIM

1. A method of treating a bacterial infection in a host comprising the step of administering to the host an effective amount of glycopeptide dimer in which two glycopeptide units are covalently linked to one another through an amine function of an amino sugar.

2. The method of Claim 1 in which both glycopeptide units are A82846B.

3. The method of Claim 1 in which both glycopeptide units are vancomycin.

4. A method of Claim 1 wherein the bacterial infection is attributable to a vancomycin-resistant-enteroccus.

5. A glycopeptide dimer in which two glycopeptide units are covalently linked to one another through an amine function of an amino sugar, for use in antibacterial therapy.

6. A glycopeptide dimer in which two glycopeptide units are covalently linked to one another through an amine function of an amino sugar, for use in antibacterial therapy against vancomycin-resistant-enterococcus.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05659

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/00, 38/12, 38/14; C07K 9/00
US CL :514/2, 8, 9; 530/317, 322, 323
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 8, 9; 530/317, 322, 323

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE (WORD AND STRUCTURE SEARCH), EMBASE, BIOSIS, MEDLINE, WPIDS. SEARCH TERMS: GLYCOPEPTIDE?, VANCOMYCIN?, A828467, DIMER?, SCHIFF BASE?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	GERHARD et al., The Role of Sugar And Chlorine Substituents in The Dimerization of Vancomycin Antibiotics. J. Am. Chem. Soc., January 1993, Vol. 115, No. 1, pages 232-237, see entire article.	5-6 ---- 1-6
X --- Y	GROVES et al, The structure of an asymmetric dimer relevant to the mode of action of the glycopeptide antibiotics. Structure, August 1994, Vol. 2, pages 747-754, see entire article.	5-6 ----- 1-6
A	BEAUREGARD et al, Dimerization and membrane anchors in extracellular targeting of vancomycin group antibiotics. Antimicrobial Agents and Chemotherapy, March 1995, Vol. 39, No. 3, pages 781-785.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search
04 JUNE 1997

Date of mailing of the international search report
20 AUG 1997

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Form PCT/ISA/210 (second sheet)(July 1992)*